Acute arterial thrombosis associated with cocaine abuse

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Purpose: **Cocaine-induced arterial thrombosis is uncommon, and most reported cases involved small-diameter vessels such as the cerebral and coronary arteries. This study was undertaken to review our experience with peripheral arterial thrombosis presumed caused by cocaine abuse.**

Methods: **Hospital records were reviewed for all patients admitted over 10 years with acute arterial occlusion involving the peripheral arterial system. Patients with confirmation of cocaine use or of its derivative, crack cocaine, within 24 hours of hospital admission formed the basis of this study. Symptoms at presentation, management, and outcome in these patients were reviewed.**

Results: **Three hundred eighty-two patients with acute peripheral arterial occlusion were identified during the study period. The presumptive diagnosis of cocaine-induced arterial occlusion was made in 5 patients (4 men, mean age 38 years). Cocaine use was achieved via intranasal inhalation in 2 patients (40%), whereas the 3 remaining patients smoked crack cocaine (60%). The mean time between cocaine use and onset of arterial thrombosis was 9.2 hours (range, 2-20 hours). Symptoms at presentation included acute limb ischemia without pedal Doppler signals (3 patients, 60%) and abdominal pain without femoral pulses (2 patients, 40%). Arterial occlusion was confirmed on angiograms in all patients, which revealed aortic thrombosis in 1 patient (20%), iliac thrombosis in 2 patients (40%), superficial femoral artery thrombosis in 1 patient (20%), and popliteal artery occlusion in 1 patient (20%). Surgical thrombectomy was successfully performed in 4 patients (80%), and 1 patient (20%) underwent successful thrombolytic therapy for femoropopliteal artery occlusion. There was no perioperative mortality. All 5 patients who were discharged were available for follow-up (mean, 36 months; range, 6-75 months). There was 1 late death from myocardial infarction. In 1 patient recurrent lower extremity arterial thrombosis developed after 28 months, which was successfully treated with thrombolytic therapy.**

Conclusions: **Our study underscores cocaine abuse as a potential cause of acute arterial thrombosis. Cocaine-induced arterial thrombosis should be suspected in patients with recent history of cocaine abuse with acute limb ischemia without an identifiable source or overt cardiovascular risk factors. Prompt angiography with operative or endovascular intervention should be performed to avert arterial ischemic sequelae. (J Vasc Surg 2004;40:291-5.)**

For many centuries coca leaves were considered an important herbal medicine among the South American native Indians residing in high-altitude terrain, who regularly chewed coca leaves to achieve a euphoric effect.[1] Over the past century, however, coca leaves have been routinely processed to produce cocaine powder, which is a highly addictive and commonly used illicit drug in the United States. It is currently estimated that more than 4 million persons in the United States use cocaine regularly, of which 1 million persons are clinically addicted to cocaine or its derivate, crack cocaine.[2]

Habitual consumption of cocaine can result in serious health hazards, particularly involving the cardiovascular system. More than 20% of patients who go to emergency rooms because of cocaine overdose had symptoms relating to the cardiovascular system.[3] Cocaine-induced cardiovascular complications are well documented, and include myocardial ischemia, cardiac arrhythmia, aneurysm rupture, aortic dissection, endocarditis, and deep venous thrombosis.[4-8] In contrast, cocaine-induced arterial thrombosis is uncommon, and most reported cases involve small-diameter vessels such as the cerebral and coronary arteries.[2,9] Arterial thrombosis involving peripheral vasculature is even rarer, and has been documented in only 3 case reports.[10-12] In this study we report our experience in patients with peripheral arterial thrombosis associated with consumption of cocaine or its derivative, crack cocaine. Symptoms at presentation, management, and outcomes in these patients are reported.

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Competition of interest: none.

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MATERIALS AND METHODS

From January 1992 to June 2003, hospital records for all patients treated at Baylor College of Medicine–affiliated hospitals because of an acute arterial thromboembolic event were reviewed. These hospitals included the Methodist Hospital, the Ben Taub General Hospital, and the Houston Veterans Affairs Medical Center. Particular attention was paid to the temporal relationship between illicit drug use and the onset of thromboembolic episodes. Patients with confirmation of cocaine use or of its derivative, crack cocaine, within 24 hours of hospital admission formed the basis of this study. In contrast, patients with certain risk factors associated with thromboembolic pro-

Table I. Clinical summary of patient characteristics, history of other illicit drug usage, and site of arterial occlusion

Patient	*Age (y)*	*Sex*	*Route and type of cocaine usage*	*History of other illicit narcotic usage*	*Duration of cocaine use and arterial thrombosis (hr)*	*Site of thrombosis*
1	26	Male	Cocaine intranasal inhalation	Marijuana, heroin	16	Aorta
2	42	Male	Smoking, crack cocaine	Marijuana, amphetamine	3	Left common iliac artery
3	49	Male	Smoking crack cocaine	Heroin, phencyclidine (PCP)	2	Right external iliac artery
4	38	Female	Cocaine intranasal inhalation	Marijuana	20	Right superficial femoral artery
5	46	Male	Smoking crack cocaine	Heroin	5	Left popliteal artery

pensity were excluded from the study. These risk factors included known arterial embolic sources, such as aortic aneurysm or valvular heart disease; documented cardiac risk factors, such as atrial fibrillation; and proved hypercoagulable states. Data were collected with respect to timing and route of cocaine usage, clinical presentation and diagnostic findings of arterial thrombosis, and intervention and treatment outcome. Long-term data were obtained from clinical or hospital records or by telephone interview with the patient or the primary physician.

RESULTS

Three hundred eighty-two patients with acute peripheral arterial occlusion were identified during the study period. A presumptive diagnosis of cocaine-induced arterial occlusion was made in 5 patients (Table I), who included 4 men and 1 woman, with mean age of 38 years (range, 26-49 years). Cocaine use was via intranasal inhalation in 2 patients (40%), whereas the remaining 3 patients smoked crack cocaine (60%). The mean time between cocaine use and onset of arterial thrombosis was 9.2 hours (range, 2-20 hours). The mean history of cocaine usage was 3.4 years (range, 0.8-7 years). In addition to using cocaine or its derivatives, all 5 patients had used other illicit narcotic drugs (Table I). No patient had a history or family history of thromboembolism.

Symptoms at presentation included acute lower limb ischemia without pedal Doppler signals (3 patients, 60%) and abdominal pain without femoral pulses (2 patients, 40%). In contrast, palpable femoral, popliteal, and pedal pulses were noted in the contralateral leg in all 5 patients. Arterial occlusion was confirmed at angiography in all patients, which revealed aortic thrombosis in 1 patient (20%), iliac thrombosis in 2 patients (40%), superficial femoral artery thrombosis in 1 patient (20%), and popliteal artery thrombosis in 1 patient (20%). Except for the patient with aortic thrombosis, the remaining patients had unilateral lower extremity ischemic symptoms. All patients underwent a thorough anticoagulation evaluation, which included the following serum levels: protein C, protein S, factor V Leiden, homocysteine, lupus anticoagulant, anticardiolipin antibody, and antithrombin III activity. Moreover, a hematology consultation was obtained to assist in the hypercoagulation workup in all patients. Transesophageal echocardiography was performed in all patients, and showed no evidence of proximal cardiac source of arterial embolism. Laboratory and diagnostic studies in these patients revealed no other cardiovascular or thrombotic risk factors that would predispose to arterial occlusion. Table II lists the treatment and outcome in these patients with cocaine-induced arterial occlusion. Surgical thrombectomy with a Fogarty embolectomy balloon via femoral artery cutdown was successfully performed in 4 patients (80%). Mean operative time was 74 minutes (range, 57-130 minutes). Completion arteriography was performed intraoperatively, and documented successful restoration of arterial flow to the pedal vessels in these patients. In contrast, 1 patient with a popliteal artery embolism (20%) underwent catheter-directed thrombolytic therapy via a contralateral femoral approach. After 24 hours of intra-arterial infusion of urokinase (Abbokinase, 1,200,000 units; Abbott), the popliteal artery circulation was successfully restored with palpable pedal pulses. All thrombi removed at surgical thrombectomy were sent to the Pathology Department for specimen analysis, which revealed platelet-rich thrombus with mixed presence of fibrin and red blood cells. Drug counseling was initiated in all patients before their discharge. All patients were treated with intravenous heparin followed by oral warfarin sodium for 6 months after the thrombectomy or thrombolysis procedure. No perioperative morbidity or mortality occurred in these patients. The mean length of hospitalization was 4.5 days (range, 2-7 days).

All 5 patients who were discharged were available for follow-up (mean, 36 months; range, 6-75 months). One patient died of drug overdose 8 months later. There was 1 late death from myocardial infarction. In 1 patient recurrent lower extremity arterial thrombosis developed after 28 months, which was successfully treated with thrombolytic therapy. At the time of the recurrent arterial thrombosis the

Table II. Treatment and outcome in patients with cocaine-induced arterial occlusion

Patient	*Initial treatment*	*Outcome after initial treatment*	*Subsequent treatment*	*Follow-up (mo)*	*Outcome and follow-up*
1	Surgical thrombectomy	Palpable pedal pulses	NA	22	Died of myocardial infarction 26 months later
2	Surgical thrombectomy	Palpable pedal pulses	NA	75	No further thrombotic episode
3	Surgical thrombectomy	Palpable pedal pulses	NA	6	Died of drug overdose 8 months later
4	Surgical thrombectomy	Palpable pedal pulses; SFA occlusion 28 months later	Thrombolytic therapy	28	Lost to follow-up after secondary treatment
5	Thrombolytic therapy	Palpable pedal pulses	NA	48	No further thrombotic episode

SFA, Superficial femoral artery; *NA,* not available.

patient denied any cocaine use. After a 5-day hospitalization, the patient was lost to subsequent follow-up.

DISCUSSION

This report is notable because it represents the largest series of patients with cocaine-induced acute thrombosis involving the peripheral arterial system. Moreover, our series highlights the relatively young age of patients with cocaine-induced arterial ischemia. The results of this study demonstrate that immediate operative or endovascular intervention can result in successful restoration of arterial circulation. Despite initially successful interventions, nonetheless, habitual consumption of cocaine in several patients likely resulted in other devastating consequences that accounted for subsequent morbidity and mortality.

As the leading cause of drug-related deaths in the United States, cocaine and its derivate, crack cocaine, are the most commonly used illicit drugs among persons seeking acute care in hospitals or drug treatment centers.[5] Cocaine is an alkaloid extract from the leaves of *Erythroxylon coca* plants growing primarily in South America. Cocaine is prepared by dissolving the alkaloid coca extracts in hydrochloric acid to form a water-soluble salt. In contrast, crack cocaine is a more potent, basic non-salt derivative of the cocaine alkaloid, which is prepared from ether solution.

Crack cocaine has gained increasing popularity among drug users, because it can be readily manufactured at home with simple laboratory apparatus.[13] Moreover, the rapid absorption of crack cocaine, when smoked, is facilitated by the large respiratory absorptive surface.[14] As a result, the effect of smoking crack cocaine is nearly instantaneous and extremely powerful. We postulate that this mechanism of pharmacologic absorption may account in part for the disparity in onset of arterial ischemia in our patients. Those patients who smoked crack cocaine experienced a more rapid onset of ischemic symptoms, in the range of 2 to 5 hours. In contrast, the 2 patients who inhaled cocaine intranasally had delayed onset of ischemic symptoms, at 16 and 20 hours, respectively. Previous studies have demonstrated that cocaine-induced arterial thrombosis in the coronary circulation is associated with early onset of symptoms, in the range of 5 to 90 minutes.[5,6,15] This rapid temporal relationship was in sharp contrast to our patients, who developed ischemic symptoms many hours after cocaine usage. We believe the delayed onset of ischemic symptoms was largely due to the diameter disparity compared with the coronary circulation. Because a coronary artery is typically less than 3 mm in diameter, rapid onset of thrombosis is more likely to develop in the event of severe vasoconstriction from cocaine ingestion. In all of our patients, on the other hand, the affected circulation was peripheral vessels, such as aortoiliac or femoropopliteal arteries, which have a much larger diameter than the coronary circulation. Therefore a much longer duration took place before arterial thrombosis occurred from cocaine-induced vasoconstriction.

We postulate that cocaine was the main cause of arterial thrombosis in our patients, as evidenced by the strong temporal relationship between cocaine consumption and onset of ischemic symptoms. It is noteworthy that none of our patients had other cardiovascular or hematologic risk factors for increased thrombotic propensity. Cocaine-induced peripheral arterial occlusion has been described in only 3 reports previously.[10-12] Chen et al[11] reported a patient who inhaled cocaine intranasally and had multiple arterial thromboses 8 hours later that involved the popliteal, hepatic, celiac, and splenic arteries. These were successfully treated with a combination of systemic anticoagulation, operative thrombectomy followed by femorotibial bypass grafting, and delayed splenectomy. Another case report described a patient in whom acute-onset lower leg ischemia developed 1 hour after smoking crack cocaine. Urgent angiography was performed, and revealed thrombosed iliac and popliteal arteries. Thrombolytic therapy was instituted, which resulted in a successful outcome.[10] Last, Webber et al[12] recently described 2 patients in whom aortic thrombosis developed after they smoked crack cocaine. One patient underwent operative aortic thrombectomy through a thoracoabdominal approach, and the other patient was treated nonoperatively with systemic anticoagulation. Both patients had a prolonged hospital course, but ultimately were discharged to home with satisfactory out-

comes. Similar to the patients in our series, these patients all underwent thorough diagnostic evaluations, which did not identify any hematologic or cardiovascular risk factors that predisposed to arterial thrombosis. More important, the strong temporal correlation between cocaine consumption and acute onset of arterial ischemia in all of these patients underscores this unusual pharmacologic cause of arterial thrombosis.

The precise mechanism of action of cocaine-induced arterial thrombosis remains poorly defined. However, cocaine exerts numerous physiologic effects, which may in part account for the ischemic complications in these patients. Illicit cocaine use has been known to result in many cardiovascular adverse effects, due largely to its central and peripheral adrenergic stimulation, which influences arterial circulation.[5] The predominant action of cocaine is inhibition of the reuptake of dopamine and norepinephrine at preganglionic sympathetic nerve endings, which potentiates the effect of endogenous catecholamines, resulting in arterial vasoconstriction and hypertension. This vasoconstrictive effect of cocaine has been confirmed in a clinical study in which quantitative coronary angiography was performed in patients after intranasal cocaine consumption.[15] The researchers found a significant reduction in coronary blood flow and luminal diameter as a result of vasoconstriction in patients treated with cocaine compared with patients treated with intranasal saline solution control.[15]

Platelet aggregation and subsequent release of its vasoactive mediators is another potential mechanism of cocaine-induced arterial thrombosis.[16] Using human platelets and animal studies, Kugelmass et al[17,18] demonstrated that intravenous cocaine administration activated circulating platelets, as evidenced by the increased expression of P-selectin, found on the surface of activated platelets. The hypothesis of cocaine-induced platelet aggregation has been similarly supported in numerous autopsy studies that demonstrated acute occlusive thrombi composed predominantly of platelets in peripheral and coronary arteries.[19-21] Last, cocaine may induce arterial thrombosis by causing endothelial cells to increase the release of endothelin, a potent vasoconstrictor, and also to decrease the production of nitric oxide, a powerful vasodilator.[5,22] Using both plethysmographic and angiographic assessment, Havranek et al[22] compared the endothelium-dependent vasorelaxation in response to intraarterial acetylcholine and nitroprusside administration in long-term cocaine users and non-cocaine users. They found significantly impaired endothelium-dependent vasorelaxation in the cocaine users compared with the control group.

Once cocaine-induced arterial thrombosis is identified, treatment strategies of thrombus removal and reestablishment of arterial circulation can be performed with either surgical thrombectomy or catheter-directed thrombolysis. In all of our patients arteriograms revealed acute thrombosis without underlying atherosclerosis or contralateral disease process. Operative thrombectomy is indicated in patients with large thrombus load or limb-threatening ischemia, which mandate immediate thrombus removal. This treatment strategy successfully restored the arterial circulation in 4 of our patients. Because balloon thromboembolectomy was used in patients with arterial thrombosis involving relatively large vessels, such as aorta, iliac, and femoral arteries, we did not observe any significant vasospasm after thrombectomy. In 1 patient with popliteal artery thrombosis we chose catheter-directed thrombolysis via a contralateral femoral approach, because of the thrombus burden in a small-caliber vessel. While this percutaneous approach provides a less invasive benefit, catheter-directed thrombolysis may also obviate the potential operative trauma associated with balloon thrombectomy. Conservative management with systemic anticoagulation may be considered in patients with no overt ischemic symptoms, which was reported to be successful in a patient with cocaine-induced aortic thrombosis.[12]

In conclusion, our study underscores that cocaine abuse is a potential cause of acute arterial thrombosis. Cocaine-induced arterial thrombosis should be suspected in patients with a recent history of cocaine use who have acute limb ischemia without overt cardiovascular risk factors. Physicians should have a high index of suspicion when treating patients with a history of illicit cocaine consumption who have arterial ischemia. With prompt diagnosis and timely intervention, adequate revascularization, with limb salvage, can be achieved in these patients.

REFERENCES

1. Heath DB. Coca in the Andes: traditions, functions and problems. RI Med J 1990;73:237-41.
2. Killam AL. Cardiovascular and thrombosis pathology associated with cocaine use. Hematol Oncol Clin North Am 1993;7:1143-51.
3. Shanti CM, Lucas CE. Cocaine and the critical care challenge. Crit Care Med 2003;31:1851-9.
4. Lisse JR, Thurmond-Anderle M, Davis CP. Deep venous thrombosis in intravenous cocaine abuse mimicking septic arthritis of the shoulder. South Med J 1991;84:278-9.
5. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. N Engl J Med 2001;345:351-8.
6. Isner JM, Chokshi SK. Cardiovascular complications of cocaine. Curr Probl Cardiol 1991;16:89-123.
7. Adkins MS, Gaines WE, Anderson WA, Laub GW, Fernandez J, McGrath LB. Chronic type A aortic dissection: an unusual complication of cocaine inhalation. Ann Thorac Surg 1993;56:977-9.
8. Bacharach JM, Colville DS, Lie JT. Accelerated atherosclerosis, aneurysmal disease, and aortitis: possible pathogenetic association with cocaine abuse. Int Angiol 1992;11:83-6.
9. Konzen JP, Levine SR, Garcia JH. Vasospasm and thrombus formation as possible mechanisms of stroke related to alkaloidal cocaine. Stroke 1995;26:1114-8.
10. Mirzayan R, Hanks SE, Weaver FA. Cocaine-induced thrombosis of common iliac and popliteal arteries. Ann Vasc Surg 1998;12:476-81.
11. Chen JC, Hsiang YN, Morris DC, Benny WB. Cocaine-induced multiple vascular occlusions: a case report. J Vasc Surg 1996;23:719-23.
12. Webber J, Kline RA, Lucas CE. Aortic thrombosis associated with cocaine use: report of two cases. Ann Vasc Surg 1999;13:302-4.
13. Latkin CA, Knowlton AR, Sherman S. Routes of drug administration, differential affiliation, and lifestyle stability among cocaine and opiate users: implications to HIV prevention. J Subst Abuse 2001;13:89-102.
14. Warner EA. Cocaine abuse. Ann Intern Med 1993;119:226-35.
15. Lange RA, Cigarroa RG, Yancy CW Jr, Willard JE, Popma JJ, Sills MN, et al. Cocaine-induced coronary-artery vasoconstriction. N Engl J Med 1989;321:1557-62.

16. Togna G, Tempesta E, Togna AR, Dolci N, Cebo B, Caprino L. Platelet responsiveness and biosynthesis of thromboxane and prostacyclin in response to in vitro cocaine treatment. Haemostasis 1985;15:100-7.
17. Kugelmass AD, Oda A, Monahan K, Cabral C, Ware JA. Activation of human platelets by cocaine. Circulation 1993;88:876-83.
18. Kugelmass AD, Shannon RP, Yeo EL, Ware JA. Intravenous cocaine induces platelet activation in the conscious dog. Circulation 1995;91: 1336-40.
19. Simpson RW, Edwards WD. Pathogenesis of cocaine-induced ischemic heart disease: autopsy findings in a 21-year-old man. Arch Pathol Lab Med 1986;110:479-84.
20. Virmani R. Cocaine-associated cardiovascular disease: clinical and pathological aspects. NIDA Res Monogr 1991;108:220-9.
21. Virmani R, Robinowitz M, Smialek JE, Smyth DF. Cardiovascular effects of cocaine: an autopsy study of 40 patients. Am Heart J 1988; 115:1068-76.
22. Havranek EP, Nademanee K, Grayburn PA, Eichhorn EJ. Endothelium-dependent vasorelaxation is impaired in cocaine arteriopathy. J Am Coll Cardiol 1996;28:1168-74.

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CORRECTION

In: "Persistent sciatic artery as collateral for an occluded iliofemoral system" (Samson RH, Showalter DP. J Vasc Surg 2004;40:183).

Due to an error during the publication process, the July 2004 cover was inadvertently published in black and white. The figure on the cover should have been in color, and the correct version is reproduced below.